

Agricultural Exposures and Cancer

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The purpose of this report is to review the literature on cancer among persons employed in agriculture, to characterize the value of this line of research, and to recommend future directions. Farmers, despite a generally favorable mortality, appear to experience elevated rates for several cancers, including leukemia, non-Hodgkin's lymphoma, multiple myeloma, soft-tissue sarcoma, and cancers of the skin, lip, stomach, brain, and prostate. The rates for several of these tumors (i.e., non-Hodgkin's lymphoma, multiple myeloma, skin, brain, and prostate) appear to be increasing in the general population. No set of established etiologic factors explains all the cancer excesses observed among farmers, although several are associated with naturally occurring or medically induced immunodeficiencies. This suggests that there may be factors in the agricultural environment that introduce immune system deficiencies. Farmers are exposed to a variety of substances that could operate through this mechanism, including pesticides, engine exhausts, solvents, dusts, and zoonotic microbes. Studies to further characterize the cancer risk among farmers, their dependents, and farm laborers, and to identify the exposures that may be involved would not only be useful in providing a safe work environment in agriculture but may furnish considerable insight into the causes for a number of tumors that are rising in incidence in the general population. — *Environ Health Perspect* 103(Suppl 8):205–208 (1995)

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Introduction

The agricultural population is large, with an estimated 2 million farmers, 2.7 million farm laborers, and perhaps 6 million family members (1). Agriculture is an important component of the national economy, and the population has some unique characteristics and exposures. Farm populations may come into contact with a variety of potentially hazardous substances, including pesticides, fertilizers, fuels and oils, engine exhausts, paints, solvents, welding fumes, dusts, and zoonotic microbes. Epidemiologic studies of agricultural populations are desirable because *a*) farmer owner/operators, farm laborers, and dependents of farmers have not been as intensely studied as many other occupational groups, and such research is necessary to ensure a safe workplace; and *b*) many exposures traditionally associated with farming are becoming more commonplace in the urban environment. Thus, investigations among farmers may provide important clues to the etiology of cancer in the general population. In this paper, we provide a brief overview

of cancer risks among farmers and suggest directions for future research.

Cancer among Farmers

In the mid-1970s, the National Cancer Institute (NCI) developed a series of maps displaying mortality patterns for specific cancers in the United States by county or state economic area (2). The map for leukemia showed a string of high-rate counties through the center of the United States, ranging from the Dakotas to Texas. This pattern suggested a role for some factors associated with agriculture because these high-rate areas generally did not include cities. A series of research projects was initiated to clarify cancer risks among farmers and to identify factors that might be involved. Occupational surveys available from many developed countries were used to evaluate the overall cancer pattern among farmers. These data indicate that farmers have a more favorable experience than the general population for many causes of death, including all causes combined, heart disease, all cancers combined, as well as cancers of the lung, bladder, liver, colon, esophagus, rectum, and kidney (3) (Table 1). Despite their overall excellent mortality, farmers from many countries tend to experience higher rates than the general population for cancers of the lymphatic and hematopoietic system, skin (melanotic and nonmelanotic), soft-tissue sarcoma, lip, prostate, brain, and stomach (3). Although the excesses for these cancers are not large in absolute terms, they are striking because they occur in an occupational group that has a low

mortality for most other causes. A review of cohort and case-control studies that provide information on cancer risk among farmers noted a similar pattern to the general surveys; i.e., lower risk from major causes of death and from many cancers than other groups but higher risks for the cancers noted above (4).

Why are these particular cancers excessive among farmers? What ties them together? Although there are no clear explanations, three findings stand out. First, these tumors are not smoking related. In fact, the smoking-related cancers tend to have lower rates among farmers than among other occupational groups. This is consistent with the lower prevalence of smoking among farmers than among the general population and many other occupational groups (5). Second, several of the cancers that are excessive among farmers show rising rates among the general population of many developed countries. These

Table 1. Causes of death showing deficits and excesses among farmers.

Deficits	Excesses
All causes	Accidents
Heart disease	Leukemia
All cancer	Non-Hodgkin's lymphoma
Cancers of the:	Multiple myeloma
Lung	Skin (melanoma and other)
Bladder	Soft-tissue sarcoma
Liver	Cancers of the:
Colon	Lip
Esophagus	Prostate
Rectum	Brain
Kidney	Stomach

Data from Blair et al. (3).

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Abbreviations used: DDT, dichlorodiphenyl-trichloroethane; DHHS, Department of Health and Human Services; NCI, National Cancer Institute.

tumors include multiple myeloma, non-Hodgkin's lymphoma, and cancers of the prostate, brain, and skin (6). Finally, several of the cancers that are excessive among farmers appear to be associated with genetic or therapeutically induced immunodeficiencies (7–12). Tumors linked to immunodeficiencies include non-Hodgkin's lymphoma, leukemia, melanoma, soft-tissue sarcoma, and cancers of the stomach, brain, and lip.

The overlap of cancers occurring excessively among farmers, cancers showing rising rates in the general population, and cancers occurring among individuals with immunodeficiencies suggests that investigations of agricultural populations may be useful to identify new factors involved in the etiology of cancer, to help explain rising rates for some tumors, and to provide leads regarding mechanisms of environmental carcinogens.

Although farmers may come into contact with a number of potentially hazardous substances, epidemiologic studies have only recently attempted to focus on specific exposures. Early investigations looked at farmers as a group or at broad subgroups of farmers defined by agricultural commodities produced. Because individuals with different farming operations can have quite diverse exposures, this approach has a limited capability to identify specific factors that may contribute to the cancer burden. More targeted investigations have focused primarily on pesticides, but other agricultural exposures such as fuels, oils, engine exhausts, organic solvents, dusts, and microbes need study.

In epidemiologic investigations focusing on pesticides, the strongest association has been between non-Hodgkin's lymphoma and phenoxyacetic acid herbicides (13–16), but leukemia has been linked with several insecticides (17), soft-tissue sarcoma with phenoxyacetic acid herbicides (18) and animal insecticides (19), ovarian cancer with triazine herbicides (20), prostate cancer with herbicides (21), and DDT with cancers of the lung (22) and pancreas (23) (Table 2). Most studies have included only men, but investigations including women have reported associations between several pesticides and non-Hodgkin's lymphoma (24) and multiple myeloma (25). Studies of women in the general population have reported an association between DDT and breast cancer (26–28). Investigations of this association among women in agriculture are needed and some are under way. High-priority research efforts for the future

Table 2. Pesticide classes associated with cancer in epidemiologic studies.

Pesticides class	Cancer
Phenoxyacetic acid herbicides	Non-Hodgkin's lymphoma, soft-tissue sarcoma, prostate
Organochlorine insecticides	Leukemia, non-Hodgkin's lymphoma, soft-tissue sarcoma, pancreas, lung, breast
Organophosphate insecticides	Non-Hodgkin's lymphoma, leukemia
Arsenical insecticides	Lung, skin
Triazine herbicides	Ovary

Data from (13–28).

include a concentration on methodologic issues in exposure assessment as well as etiologic concerns.

Exposure Assessment

The major limitation to date in investigations of cancer among agricultural populations is the lack of detail regarding exposure. Often, no specific exposure assessment is undertaken and analyses are based simply on the job title farmer. This does not allow identification of specific factors that may be related to the development of cancer and tends to introduce confusion because disease risks are often compared between farmers with radically different exposure patterns. Since different farming operations may yield quite diverse exposures, simply comparing farmers overall, or broad subgroups of farmers, introduces exposure misclassification, which decreases study power and tends to bias risk estimates toward the null, thus diminishing opportunities to identify etiologic factors. More detailed assessment of exposures is needed in the future.

Assessment of historical exposures is always difficult in epidemiologic studies. At first glance, it may appear that reconstructing agricultural exposures would be particularly problematic. However, exposure assessment in agriculture may be no more difficult to assess than many lifestyle or other occupational factors. In fact, studies of farmers probably offer special advantages, particularly when exposures are based on interview data. Farmers are very knowledgeable about chemicals they use. In many industrial situations, management makes decisions regarding the selection and purchase of materials, while labor actually uses them. In such situations, neither management nor labor is familiar with all aspects of the operation. On many family farms, unlike in most industries, the farmer represents both labor and management and is engaged in the selection, purchase, and

use of farm chemicals. For pesticides, the farm owner/operator decides if there is a pest problem, determines when to treat the problem, selects the pesticide, applies the chemical, checks the results of the treatment, and records the purchases (this is a tax-deductible expense). These activities reinforce memory, which enhances the reliability and validity of information obtained by interview.

There is also an impression that farmers use so many pesticides and change chemicals so frequently that recall must be poor. This is not the case for many farmers. In several NCI surveys, the total number of pesticides used over a farmer's lifetime averaged less than 10 and, typically, the same ones were used year after year (29). Thus, the number of chemicals used seems amenable to recall. This is not to say, however, that improvements in assessment of pesticide exposures are not needed.

It may be more difficult to reconstruct pesticide exposure histories for agricultural workers who are not farm owner/operators. For example, migrant and seasonal workers are unlikely to know which pesticides have been applied to the fields where they work. It is clear that different approaches must be developed to assess exposures in this group (30).

The experimental and epidemiologic evidence suggests that potentially carcinogenic pesticides are not likely to be limited to any particular chemical class (31). To date, too few epidemiologic investigations have attempted to obtain information on individual pesticides. This must be the focus in the future. Exposure assessment can be improved by collecting information from several sources (e.g., interviews with farmers and suppliers), reviewing records (farmers are now required to keep records of pesticide purchases), conducting exposure monitoring during application, and obtaining blood or urine specimens for assessment of dose. Interviews should probe for information on specific pesticides and amounts used, mixing and application procedures, and types of protective equipment and actions used.

No one particular exposure assessment approach is likely to be universally successful in all situations. It may not be possible to achieve the desired degree of quantification of exposure simply from interviews and records. Environmental and biologic monitoring provides such quantification but only for a very short period (usually days). Farming activities resulting in exposures are often limited to relatively brief

time periods during the year; thus, when the monitoring occurs is critical. The use of detailed questionnaires supplemented with monitoring and other information together would allow a more accurate classification of relative exposure.

Pesticides understandably have been suspected of causing cancer in agricultural populations because a number of these chemicals are carcinogenic in laboratory bioassays. The mechanism of action of pesticides, however, is not well understood. Although some pesticides have genotoxic effects (32), others may cause immune system defects (33). For example, it has been proposed that organophosphate insecticides may play a role in oncogenesis through their inhibition of serine esterases, which are necessary for functioning of T-lymphocytes and natural killer cells (34). Engine exhausts may also affect the immune system because polycyclic aromatic hydrocarbons have been associated with depression of serum IgG and IgA levels (35). Stimulation of the immune system through exposure to mycotoxins also appears worthy of study (36). Investigations of agricultural exposures that incorporate biologic marker components are needed to characterize potential environmental hazards faced by the agricultural and general population.

Efforts must also be undertaken to obtain information on exposure to potential agricultural hazards other than pesticides. The epidemiologic research to date has focused on pesticides, but it is time to pay attention to engine exhausts, fuels and oils, dusts, fertilizers, and zoonotic viruses. Efforts to better characterize exposures from drinking water are also needed, as contamination of drinking water by agricultural fertilizers and pesticides represents a growing problem in many areas of the country, particularly in agricultural areas (37).

Epidemiologic Investigations

Most epidemiologic investigations to date have focused on farm owner/operators and have mainly included men. Additional

work on this population is warranted because few studies so far have attempted to assess cancer risks from specific agricultural exposures. Long-term prospective studies should be considered in addition to case-control designs. Future efforts, however, must also be expanded to include evaluation of cancer risks among other groups in the agricultural setting, i.e., spouses, children, and laborers.

The role of spouses in the farming operation varies. Some wives are fully engaged in all activities and may perform the same tasks as their husbands. Investigation of cancer risks among this population is important to assess risks for female-related tumors from agricultural exposures. A study of women farmers is also important to determine whether cancer risks from agricultural exposures vary by gender. Such differences could occur because of anatomical and physiologic differences between the sexes (38) or because different approaches to job tasks result in disparate exposures.

Some spouses do not actually engage in farm activities that require direct contact with farm chemicals, but because they live on the farm (which is like living at the factory in other industries), indirect exposure is possible. For example, the potential for contamination of vehicles, furniture, and clothing may provide exposure opportunities to pesticides used on the farm to family members not directly engaged in application. This level of exposure, although it may be considerably less than that of farm operators, may equal or exceed exposure levels experienced by the general public. Studies of farm spouses could provide valuable information regarding cancer risks to the general population from such indirect exposures. Farm children may also experience direct and indirect exposures at ages when they may be especially susceptible.

Farm laborers such as seasonal and migrant workers may also experience unique exposure scenarios that put them at special risk (30). Exposures may occur at a young age because children work in the

fields or must accompany their parents to the fields because of the lack of child care facilities. Lack of protective equipment and prompt access to showers and laundry facilities (39) may exacerbate hazards by prolonging the time during which pesticides are in contact with the skin.

There is growing concern over contamination of food and drinking water with agricultural chemicals. Studies of agricultural populations may offer special advantages to address this issue. For example, the level of contamination of drinking water is greater in private wells than in public water systems, and farms often use private wells as their water source. This, plus the residential stability of farm families, offers distinct advantages over urban areas for the study of cancer risks from chemical contamination of drinking water.

It is important to remain alert for unusual exposure situations that may provide unique opportunities to evaluate cancer risks from specific agricultural chemicals. For example, studies of cancer risks among persons engaged in fruit and vegetable production have not been conducted. The intense use of pesticides, particularly fungicides, on these commodities underscores the need for evaluation. Studies of workers in hothouses producing flowers and vegetables could be informative because of heavy exposures from the use of chemicals within a confined space. Special opportunities may exist in other countries where pesticides are used more heavily and exposures may be considerably higher than in the United States.

Conclusion

Studies of cancer risk among agricultural populations will improve health and safety among this important segment of the population. These investigations may also alert us to possible hazards to the general population, identify factors contributing to the rising incidence of some cancers, and provide clues to carcinogenic mechanisms.

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